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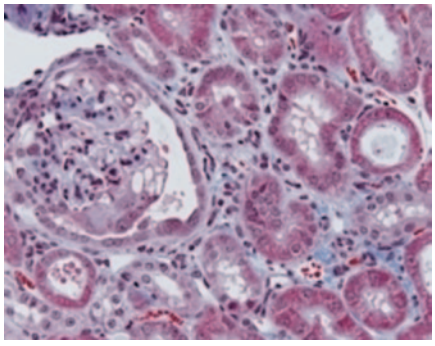
Divergent roles of Smad3 and PI3-kinase in murine adriamycin nephropathy indicate distinct mechanisms of proteinuria and fibrogenesis



Proteinuria is a strong predictor of chronic kidney disease (CKD) progression, and renal fibrosis occurs in nearly all forms of progressive CKD. Many studies have implicated a central role for transforming growth factor-β (TGF-β) in promoting glomerular disease and renal fibrosis. In this issue, Finer *et al.* report studies using a novel murine adriamycin nephropathy model of focal glomerulosclerosis. They found that TGF-β inhibition ameliorated renal fibrosis in adriamycin-treated mice without reducing proteinuria. Further studies revealed that early podocyte injury and subsequent proteinuria were characterized by activation of the p110γ isoform of PI3-kinase and that administration of a specific inhibitor of p110γ reduced adriamycin-induced proteinuria *in vivo* but had no effect on TFG-β-induced fibrogenesis *in vitro*. These studies demonstrate that proteinuria and fibrosis in glomerular disease may occur via distinct mechanisms. **See page 525.**

The early decline in renal function in patients with type 1 diabetes and proteinuria predicts the risk of end-stage renal disease

Though previous studies have demonstrated that patients with type 1 diabetes mellitus and proteinuria are at increased risk of end-stage renal disease (ESRD), clinicians cannot accurately predict their rate of decline in glomerular filtration rate. Skupien *et al.* followed a cohort of 161 patients with type 1 diabetes mellitus, proteinuria, and estimated glomerular filtration rate (eGFR) ≥ 60 ml/min at baseline for 5–18 years. They found the eGFR decline slow and the ESRD risk minimal in more than one-third of patients. However, in the remaining patients, the rate of decline and ESRD risk were more variable. Importantly, the investigators demonstrated that the rate of decline in eGFR during the first 5 years of follow up in patients with type 1 diabetes mellitus and proteinuria strongly predicted subsequent risk of ESRD. **See page 589.**

Vitamin K intake and status are low in hemodialysis patients

Vitamin K-dependent carboxylation is required for the normal function of proteins with γ-carboxyglutamate (Gla) residues, including matrix Gla protein (MGP), the strongest known inhibitor of vascular calcification. Cranenburg and colleagues studied dietary vitamin K intake in a cohort of hemodialysis patients and correlated dietary vitamin K with plasma levels of non-carboxylated Gla-containing proteins. Hemodialysis patients had markedly lower vitamin K intake compared with healthy controls and also had much higher levels of non-carboxylated Gla proteins, including MGP. This valuable study suggests that low dietary vitamin K may be an important contributor to vascular calcification in patients receiving hemodialysis. **See page 605.**